

**REMARKS**

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 5-11 are in this case. Claims 5- 11 have been rejected. Claims 5-11 have now been cancelled. New claims 14-26 have now been added. An Abstract of the disclosure on a separate sheet, as required by the Examiner, is attached herein.

***35 U.S.C. § 112 Second Paragraph Rejections***

The Examiner has rejected claims 5-11 under 35 U.S.C. § 112, Second Paragraph, as being indefinite for failing to point out and distinctly claim the subject matter of the invention. Claims 5-11 have been cancelled, rendering moot the Examiner's rejection thereof. New claims 14- 26 have been added.

The Examiner states that claims 5-6 and dependents are indefinite in their recitation of "somewhat valuable", and that claims 7-11 are indefinite in their recitation of "method or construct according to claims 5 or 6...". Claims 5-11 are now cancelled, and have been replaced with independent claims 14 and 19 and claims depending therefrom.

To further clarify and define the scope of the present invention, and to expedite prompt prosecution of this case, Applicant has chosen to cancel claims 5-11, and replace them with new claims 14-26. Independent new claims 14 and 19 replace cancelled claims 5 and 6, respectively, and recite at least one "genetically engineered, commercially desirable genetic trait" and at least one "...genetically linked, mitigating genetic trait being benign or desirable to the cultivated crop...". The mitigating genetic trait is further limited by the recitation: "...wherein said mitigating genetic trait is selected such that an undesirable, uncultivated interbreeding species related to the cultivated crop expressing said mitigating genetic trait is less fit than an undesirable, uncultivated interbreeding species related to the cultivated crop not expressing said mitigating genetic trait..." in both claim 14 and 19, thus replacing the terms deemed as indefinite by the Examiner in now cancelled claims 5 and 6. The term "commercially desirable" is an art recognized term defined throughout the instant specification, for example, page 6, lines 5-18, and page 6, line 26 to page 7, line 2. The term "weed" of the original claim has now been replaced with the more

definite phrase "...an undesirable, uncultivated interbreeding species related to the cultivated crop...". Support for this phrase can be found throughout the instant specification: for example, a "weed" is clearly defined as "undesirable plant(s) growing wild, especially those growing on cultivated ground to the disadvantage of the crop" (page 7, lines 3-6), and "forms that have escaped cultivation,... that have evolved weedy characters,...and...volunteer weeds" (page 7, lines 6-10); and it is clearly stated that the introgression of genetically engineered traits is a danger among "...interbreeding relatives" of crops (page 2, line 22).

Further, the Examiner has stated that claims 7-11 are indefinite in their apparent dependence on both processes (methods) and products (constructs). Applicant wishes to point out that claims 7-11 have now been cancelled, and replaced by new dependent claims 15-18 which relate solely to new independent method claim 14, and new dependent claims 20-24, which relate solely to independent claim 19, separating between claims reciting a product (claims 19-26), and those reciting a process of the present invention (claims 14-18), as recommended by the Examiner.

In view of the newly drafted claims mentioned above, Applicant believes to have overcome the 35 U.S.C. § 112 Second Paragraph rejections.

#### ***35 U.S.C. § 112 First Paragraph Rejections***

The Examiner has rejected claims 5-11 under 35 U.S.C. § 112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention. Claims 5-11 have been cancelled, rendering moot the Examiner's rejection thereof. New claims 14- 26 have been added.

The Examiner states that the claims are broadly drawn to constructs comprising a multitude of sequences and from a multitude of sources, conferring traits deleterious to weeds such as abolished secondary dormancy, uniform or delayed ripening, anti-shattering, dwarfism, etc., and methods of using such constructs to transform plants, while the specification provides no guidance regarding the isolation of any gene or gene product conferring such traits.

Applicant wishes to point out that the present invention is of a method of obtaining a crop capable of mitigating the effects of intra- or interspecies introgression of genetically engineered trait(s) between the transgenic crops and potential interbreeding weeds, and of genetic constructs, for preventing accidental genetic transfer of advantageous traits such as herbicide resistance, environmental stress resistance, high productivity, etc. to undesirable species of the crop, weeds or wild species. As described extensively in the instant specification, this novel method represents a revolutionary departure from previously conceived efforts to contain such undesirable genetic transfer of genetically engineered traits into potential interbreeding material, in that fundamental differences between crop cultivation and weed growth are identified, and exploited, to the disadvantage of the undesirable interbreeding weed. Previous containment efforts have depended upon inefficient traditional means such as isolation distances (isolation zones) (see Ritala A., et al, Crop Sci 2002;42:278-85, abstract provided) and barrier crops (see Physical Gene Flow Barriers, page 61; in: Environmental issue report, No. 28, European Environmental Agency Publication No. 28, 2002), less conventional, but still problematic biological means such as apomixis, cleistogamy, male sterility and plastid transformation (see Biological Gene Flow Barriers, pages 60 and 61; in: Environmental issue report, No. 28, European Environmental Agency Publication No. 28, 2002) and the highly complex and uneconomical introduction of lethal traits under control of inducible promoters (see Kuvshinov VV et al, Plant Sci 200;160:517-522, abstract provided, and US Pat No. 5,723,765 to Oliver et al).

Further, Applicant wishes to point out that the Written Description Requirement, as defined in the guidelines, need not provide description of all possible species of a claimed genus but rather merely identify characteristics of a species in a manner which illustrates to the ordinary skilled artisan that the inventor was in possession of the invention at the time of filing.

Such characteristics are provided in the instant application (see, for example, page 11, lines 8-18, and page 17, line 4 to page 19, line 16, page 21, line 36 to page 24, line 31), and thus provide an ordinary skilled artisan with appropriate guidelines for practicing the full scope of the claimed invention. It will

be appreciated in this case that since the problem of gene flow from crops to undesirable interbreeding variants (i.e. weeds, wild species) differs in character for each crop-and-weed combination, selection of the commercially desirable and mitigating genetic traits for a specific crop-weed combination according to the guidelines set forth in the instant application must be effected on an individual, rather than generalized basis. However, since guidelines for such selection are clearly identified in the instant application, one of ordinary skill in the art would instantly recognize commercially desirable and mitigating genetic traits suitable for mitigation of introgression in a specific crop-weed combination of interest.

Examples of such crop-and-weed combinations such as rice and red rice, sugar beet and wild sugar beet, etc. are well known in the art (see for example, Crop-to-Weed Gene Flow in Transgenic Crops: An Introduction and Resource Guide, [www.colostate.edu/programs/lifesciences](http://www.colostate.edu/programs/lifesciences), copy provided, and Genetically Modified Organisms: The significance of gene flow through pollen transfer, in European Environmental Agency Publication No. 28, 2002). Important factors to be considered in formulating effective anti-introgression strategies for individual crop-and-weed pairs include factors affecting pollen dispersal and cross pollination, likelihood of hybridization and gene flow, and the hardiness of the hybrid plants. However, to the extent that such factors are known, one of ordinary skill in the art would readily recognize the methods and constructs of the present invention to prevent introgression of genetically engineered traits from crops to undesirable interbreeding related species, without undue experimentation.

The method of the present invention exploits close genetic linkage to ensure the tandem introgression, if such should occur, of crop-advantageous and non-crop, disadvantageous traits to potential interbreeding weeds. Advantageous and desirable first genetic traits are well known in the art- herbicide resistance, increased productivity, etc- and are described in detail throughout the instant specification (see, for example page 11, lines 8-18). In addition, many of the genes responsible for such traits are also known in the art, and have been effectively used in to produce improved transgenic plants, such as MAPK phosphatase for improved yield (U.S. Pat No. 6548743 to Sheen et al), genes governing increased starch content (U.S. Pat No. 638178 to Kishore), increased cold tolerance (U.S. Pat No. 6501006 to Ismail et al),

pathogen resistance proteins (U.S. Pat No. 6376747 to Bidney et al) and genes governing water stress resistance (U.S. Pat No. 6229069 to Yamada), and many others.

While in theory, many traits can be commercially desirable, the instant specification provides clear and precise guidelines as to what constitutes the commercially desirable genetic trait as recited in the instant specification and claims (see for example, page 17 lines 4-38 and page 20, lines 3-4 and 13-14). The choice of mitigating genetic traits "being benign or desirable" to the cultivated crop, and "selected such that an undesirable, uncultivated interbreeding species related to the cultivated crop expressing said mitigating genetic trait is less fit than undesirable, uncultivated interbreeding variety of the cultivated crop not expressing said mitigating genetic trait...", as recited in new, independent claims 14 and 19, must also be made within the context of the individual crop- and- weed combination. Such a mitigating genetic trait, chosen from defined plant characteristics well known in the art, can be selected using the guidelines provided in the instant specification: "Because weeds have strong competition amongst themselves, and have large seed output...even mildly deleterious traits are quickly eliminated from populations" (page 16, lines 19-21). Thereinafter ensues a detailed account of how specific examples of such mitigating genetic traits, such as lack of secondary dormancy, anti-shattering or dwarfing, can be suitable for use in specific embodiments of the present invention, according to the particular crop-weed combination being considered (pages 17, line 4, to 19, line 14). Thus, one of skill in the art in possession of the teachings of the present invention could certainly be able to "visualize or recognize the identity of..." such commercially desirable and mitigating genetic traits as recited in instant claim 14 and 19.

Indeed, employing the methods described in the instant specification, Al-Ahmad et al have recently produced transgenic tobacco plants having tandemly linked herbicide and semi-dwarfism genes. Stable, genomic expression of the *ahas*<sup>R</sup> gene conferred resistance to imidizolinone herbicides, but the stunted stature conferred by the semi-dwarfism *Δgai* gene resulted in decreased survival when co-cultivated among wild-type segregants (see attached Appendix and Declaration). The reduced competitive ability was expressed in very low survival rates of the transgenic

plants, and non-flowering among the few surviving transgenic individuals. This simulates the fate of crop-weed hybrids resulting from unintended introgression of a construct of the present invention to an undesirable, uncultivated interbreeding variety of a cultivated crop (tobacco, in this case), when competing with wild-type weeds, or such crops as volunteer weeds, when the selector herbicide is not present.

In order to further define and clarify the present invention, and to expedite the prompt prosecution of this case, Applicant has chosen to replace now cancelled claims 5 and 6 with new independent claims 14 and 19, contain the limitation: "at least one mitigating genetic trait being benign or desirable to the cultivated crop...selected such that an undesirable, uncultivated interbreeding species related to the cultivated crop expressing said mitigating genetic trait is less fit..." (emphasis added), thereby restricting the invention as now claimed to: 1) crop-weed pairs of cultivated crops and undesirable, uncultivated interbreeding species related thereto; 2) mitigating genetic traits being benign or desirable to the specific crop of the specific crop-weed pair; and 3) mitigating genetic traits conferring reduced fitness on specific weeds of the specific crop-weed pair. Thus, it is Applicant's strong opinion that new claims 14 and 19, and claims dependent therefrom, now more clearly define the scope of the present invention, and as such overcome the Examiner's rejection under 35 U.S.C. § 112, First Paragraph.

The Examiner has further rejected claims 5-11 under 35 U.S.C. § 112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claims 5-11 have been cancelled, rendering moot the Examiner's rejection thereof. New claims 14- 26 have been added.

The Examiner states that the claims are broadly drawn to constructs comprising a multitude of sequences and from a multitude of sources, conferring traits innocuous to crop plants but deleterious to weeds such as abolished secondary dormancy, uniform or delayed ripening, anti-shattering, dwarfism, etc., and methods of using such constructs to transform plants, while the specification provides no guidance regarding the isolation of any gene or gene product conferring such traits, crop plant transformation evaluation of the putative genes to confer the traits, or regarding the identification of any weedy species or transformation therewith to

confer a deleterious trait thereto. Further, the Examiner decries the paucity of "currently available isolated genes... encoding any or all proteins... deleterious to weeds..."

As is discussed hereinabove, the definition of a weed as "undesired vegetation" is well known in the art (see, for example, U.S. Pat. Nos. 6,306,458 and 6,534,444 to Volrath et al, and Sievervich et al, respectively). In this context, the Examiner states that "what constitutes a trait deleterious to a weed will depend upon the particular crop plant species and the particular weed species, as well as fluctuating environmental stressors". However, to the extent that such factors are known, one of ordinary skill in the art would readily recognize the methods and constructs of the present invention to prevent introgression of genetically engineered traits from crops to undesirable interbreeding variants, without undue experimentation.

For example, the Examiner states that Desplanque teaches that bolting, rather than being deleterious, is an attractive trait for weed beets, and that Bartsch et al describes hybrids that have less bolting, but still bolt. Regarding the specific trait of bolting, Applicant wishes to point out that in the instant specification, bolting is recited in the context of a trait to be prevented in weeds (and weed beets) (see, for example, page 19, lines 2-5, "prevention of bolting", and page 23, lines 18-37, "preventing the biosynthesis of gibberellins...") such that the mitigating genetic trait is, for example, expression of an antisense, RNAi, etc. nucleic acid for disruption of bolting gene expression.

Further, the Examiner has stated that Bartsch et al teach that the BNYVV coat protein is only conditionally advantageous to sugar beets. Applicant wishes to point out that virtually all primary traits transformed into plants, just as nearly all selected mutants, confer a minimum of unfitness in the absence of specific selection pressure, which is offset by the commercial advantage when such selection pressure exists. For example, Triazine resistant oilseed rape has a genetically lower yield (15-20% lower) than that of wild type, but is of great commercial desirability due to the inexpensive herbicide that can be used.

Regarding the unpredictability of modification of deleterious traits, it is the Applicants strong opinion that the Examiner has misinterpreted the results presented

in Linder and Landbo et al. Linder tested the effect of HL transgenic construction on seed dormancy and germination in *B. rapa* x *B. napus* hybrids, and reported that maternal effects on seed germination were less prominent than expected in the hybrids. Likewise, Landbo et al found that seed germination in crop-weed hybrids of *B. campestris* x *B. napus* exhibit less maternal influence than expected. However, the crop parent did not bring loss of dormancy to the hybrids, and the crop contained no tandemly linked "loss of dormancy genes", as the crop contained no tandemly linked transgenes controlling the trait under investigation. Regarding dormancy, the instant specification recites the consideration of disrupting secondary dormancy as an example of a mitigating trait "neutral to crops but deleterious to weeds" (page 17, lines 17-18).

The Examiner has stated that Young and Oard et al teach that genetic modification of seed shattering is unpredictable. Applicant wishes to point out that the cited references are not relevant for the present invention as claimed. The present invention describes a method and constructs for obtaining a cultivated crop capable of mitigating the effects of introgression of desirable genetically engineered traits into undesirable uncultivated interbreeding varieties. Although Young reports low heritability of phenotypic trait of SR in Kleingrass, there is no discussion of the fate of transgenic or tandemly linked transgenic anti-shattering genes. Regarding Oard et al, the cited reference reported on the heritability of a genetically engineered herbicide resistance trait in hybrid crop-weed populations of cultivated rice and red rice. No tandemly linked constructs comprising shattering-related and herbicide resistance genes were described. Thus, the shattering and dormancy of the hybrids was a function of mixing of endogenous, naturally-occurring genes, and cannot be expected to reflect the results of a combination of, for example, herbicide resistance and an anti-shattering trait on introgression of the herbicide resistance into hybrid crop-weed populations.

The Examiner has further stated that the instant specification provides no guidance regarding identification, isolation and transformation with any genes to confer traits which are "innocuous or somewhat valuable", or the identification of any weedy species to confer a deleterious trait thereto. In stark contrast to the Examiner's contention, Applicant wishes to point out that the instant specification



abounds with descriptions of crop-weed pairs of commercial importance (see, for example, page 1, lines 16-36, page 6, lines 21-23, page 16, lines 27-35, page 18, line 36 to page 19, line 14, 21, lines 14-34, and page 22, lines 20-25). The identification of candidate genes encoding "introgression-mitigating" traits, as described in the instant specification, is discussed hereinabove.

Further, Applicant wishes to point out the recent successful demonstration of mitigation of introgression of transgenic herbicide resistance in tobacco plants transformed with a tandemly-linked construct according to the teachings of the present invention, striking evidence of the ability of one skilled in the art to make and use the present invention as described, without undue experimentation (see above, and attached Appendix and Declaration).

The abovementioned notwithstanding, in order to further define and clarify the present invention, and to expedite the prompt prosecution of this case, Applicant has chosen to replace now cancelled claims 5 and 6 with new independent claims 14 and 19, contain the limitation: "a...mitigating genetic trait being benign or desirable to the cultivated crop...selected such that an undesirable, uncultivated interbreeding species related to the cultivated crop expressing said mitigating genetic trait is less fit..." (emphasis added), thereby restricting the invention as now claimed to: 1) crop-weed pairs of cultivated crops and undesirable, uncultivated interbreeding species related thereto; 2) mitigating genetic traits being benign or desirable to the specific crop of the specific crop-weed pair; and 3) mitigating genetic traits conferring reduced fitness on specific weeds of the specific crop-weed pair. Thus, it is Applicant's strong opinion that new claims 14 and 19, and claims dependent therefrom, are now directed to a more clearly defined group of genes conferring "mitigating" traits, in specific crop-weed pairs.

In view of the objective evidence and new claims described hereinabove, Applicant believes to have overcome the Examiner's rejection under 35 U.S.C. § 112, First Paragraph.

**35 U.S.C. § 102(b) Rejections – Klee et al., Yanofsky et al., Schaller et al, WO 96/34088 (COLD SPRING HARBOR), and Wang et al.**

The Examiner has rejected claims 5,6 and 8-11 under 35 U.S.C. § 102 (b) as

being anticipated by Klee et al. (US 5,512,466), Yanofsky et al. (US 6,198,024), Schaller et al. (Plant Physiol, 1998; 118: 461-69), WO 96/34088 (COLD SPRING HARBOR, Colisanti et al), and Wang et al. (Cell, 1998; 93:1207-217). The Examiner's rejections are respectfully traversed. Claims 5-11 have been cancelled, rendering moot the Examiner's rejections thereof. New claims 14-26 have been added.

The Examiner points out that the claims are broadly drawn to a genetic construct comprising a gene encoding a first trait linked to a gene encoding a second trait, which second trait is innocuous to a crop species but deleterious to a weed, and methods for the transformation of crop plants therewith, wherein the second trait includes, inter alia, delayed ripening, anti-shattering, dwarfism and non-flowering.

Applicant wishes to point out that the present invention is of a method of obtaining a crop capable of mitigating the effects of intra- or interspecies introgression of genetically engineered trait(s) between the transgenic crops and potential interbreeding weeds, and of genetic constructs, for preventing transfer of advantageous traits such as herbicide resistance, environmental stress resistance, high productivity, etc. to undesirable varieties of the crop. The method of the present invention exploits tight genetic linkage, either physical or functional, to ensure the tandem introgression, if such should occur, of crop-advantageous and non-crop disadvantageous traits to potential interbreeding weeds. Thus, the methods and constructs of the present invention recite a "first genetic trait of a crop", relating to an advantageous, commercially desirable trait introduced by genetic manipulation, and a "mitigating genetic trait being innocuous or somewhat valuable to the crop yet deleterious to the weed", introduced in tandem with the first genetic trait.

In contrast to the constructs of the present invention, all five of the cited prior art references describe nucleic acid constructs comprising a gene encoding a plant-functional trait (delayed ripening, anti-shattering, dwarfism, etc) linked to a gene conferring kanamycin resistance. Applicant wishes to point out that resistance to the aminoglycoside antibiotic kanamycin, conferred by a nucleic acid "cassette" spliced into transformation vectors and extensively used as a selectable marker of gene expression in transformed cells is not, and cannot be considered in any combination, an advantageous, commercially desirable gene of a crop, kanamycin having no

known commercial application in plants (“...a transgenic plant or any other organism that might have acquired the gene (*kan<sup>R</sup>*) will not get any selective advantage because of this gene.” from Nap et al, Transgenic Res. 1992, 6:239-49). Thus, all of the prior art constructs reading on kanamycin-linked traits, fail to anticipate the tandemly linked genetic constructs of the present invention.

The abovementioned notwithstanding, in order to further define and distinguish the present invention from the prior art, and to expedite the prompt prosecution of this case, Applicant has chosen to replace now cancelled claims 5 and 6 with new independent claims 14 and 19, respectively, containing the limitations: “...at least one genetically engineered, commercially desirable genetic trait” and at least one “...genetically linked, mitigating genetic trait being benign or desirable to the cultivated crop...” the mitigating genetic trait further limited by the recitation: “...wherein the mitigating genetic trait is selected such that an undesirable, uncultivated interbreeding species related to of said crop expressing said mitigating genetic trait is less fit than an undesirable, uncultivated interbreeding species related to the cultivated crop not expressing said mitigating genetic trait...” thereby restricting the invention as now claimed to: 1) genetically engineered, commercially desirable genetic traits; 2) mitigating genetic traits being benign or desirable to the specific crop of the specific crop-weed pair; and 3) mitigating genetic traits conferring reduced fitness on uncultivated, undesirable interbreeding species related to the cultivated crop (weeds). Thus, the phrase “genetically engineered genetic trait of a crop” now includes the phrase “commercially desirable”. “Commercially desirable” is an art recognized term defined throughout the instant specification, for example, page 6, lines 5-18, and page 6, line 26 to page 7, line 2. The phrase “genetically linked mitigating genetic trait...said mitigating genetic trait being innocuous or somewhat valuable to the crop, yet deleterious to the weed.” of the original claim has now been replaced with the more definite phrase “...at least one genetically linked, mitigating genetic trait being benign or desirable to the cultivated crop, wherein the mitigating genetic trait is selected such that an undesirable, uncultivated interbreeding species related to the cultivated crop expressing said mitigating genetic trait is less fit than an undesirable, uncultivated interbreeding species related to the cultivated crop not expressing said mitigating genetic trait...”.

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more clearly defining the mitigating genetic trait in terms of function when expressed in a weed, i.e. "an undesirable, uncultivated interbreeding species related to said crop...". Thus, it is Applicant's strong opinion that new claims 14 and 19, and claims dependent therefrom, now more clearly distinguish the present invention from the cited prior art, and as such overcome the Examiner's rejection under 35 U.S.C. § 102, (b).

*New Claims*

New claims 14-26 have been added. Addition of these claims does not constitute addition of new material.

In view of the above amendments and remarks it is respectfully submitted that new independent claims 14 and 19, and claims 15-18, 20-26 directly or indirectly depending therefrom are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein

Registration No. 25,457

Date: May 15, 2003.

**Enclosed:**

Two month extension fee.

Cited references: Kuvshinov et al.

Ritala et al

Crop-to-Weed Gene Flow in Transgenic Crops

Appendix: Al-Ahmad et al

Declaration of Prof. Jonathan Gressel